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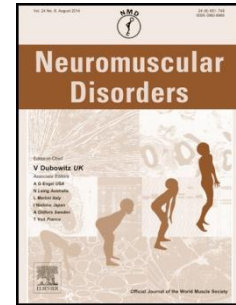
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# Compound heterozygous *RYR1* mutations in a preterm with arthrogryposis multiplex congenita and prenatal CNS bleeding

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## Highlights

- RYR1 mutations may be associated with arthrogryposis multiplex congenita.
- Compound heterozygous malignant hyperthermia mutations cause myopathic phenotype.
- Bleeding tendency should be anticipated with RYR1 genotypes.

## Abstract

*RYR1* mutations, the most common cause of non-dystrophic neuromuscular disorders, are associated with the malignant hyperthermia susceptibility (MHS) trait as well as congenital myopathies with widely variable clinical and histopathological manifestations. Recently, bleeding anomalies have been reported in association with certain *RYR1* mutations. Here we report a preterm infant born at 32 weeks gestation with arthrogryposis multiplex congenita (AMC) due to compound heterozygous, previously MHS-associated *RYR1* mutations, with additional signs of prenatal hemorrhage. The patient presented at birth with multiple joint contractures, scoliosis, severe thoracic rigidity and respiratory failure. He continued to depend on mechanical ventilation and tube feeding. Muscle histopathology showed a marked myopathic pattern with eccentric cores. Interestingly, the patient had additional unusual prenatal intraventricular hemorrhage, resulting in post-hemorrhagic hydrocephalus as well as epidural hemorrhage affecting the spinal cord. This report adds to the phenotypic variability associated with *RYR1* mutations, and highlights possible bleeding complications in affected individuals.

## Keywords

ryanodine receptor; RYR1; myopathy; arthrogryposis; CNS bleeding; malignant hyperthermia susceptibility trait

## Introduction

Arthrogryposis multiplex congenita (AMC) is due to a wide range of neurological and neuromuscular causes, the latter comprising a wide spectrum of genetically heterogeneous congenital myopathies [1]. In addition to skeletal deformities such as multiple contractures, scoliosis and thoracic deformities, severely affected newborns may present with additional respiratory insufficiency, facial weakness, swallowing problems, and severe muscular hypotonia (as well as hypertonic muscle tone in extremely rare cases) [2-4]. The risk for intrauterine death as a consequence of severe fetal akinesia is well documented [5]. Muscle biopsy and confirmatory genetic testing are diagnostically most relevant, although non-specific myopathic changes may delay the correct diagnosis in newborns and young infants [1, 6]. Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene, encoding the principal sarcoplasmic reticulum (SR)  $\text{Ca}^{2+}$  release channel with a crucial role in excitation-contraction coupling (ECC), are increasingly recognized as a common cause of various congenital myopathies [2, 7-8]: Whereas dominant mutations affecting mutational hotspots within the *RYR1* gene are mainly associated with the malignant hyperthermia susceptibility trait (MHS), a pharmacogenetic predisposition to severe adverse reactions in response to halogenated anaesthetics and muscle relaxants (for review [9]), and the congenital myopathy Central Core Disease (CCD) [10], recessive mutations distributed throughout the *RYR1* coding sequence give rise to a wide clinical-pathologic spectrum including Multi-minicore Disease (MmD) [11], Centronuclear Myopathy (CNM) [12], and Congenital Fiber Type Disproportion (CFTD) [13].

Most patients with *RYR1*-associated myopathies present in infancy or early childhood with mild or moderate muscular hypotonia and motor developmental delay. In

addition, adult myopathic presentations [14-15] such as late-onset axial myopathy [16-17], or induced manifestations such as exertional myalgia/rhabdomyolysis (ERM) [18] are increasingly recognized, in particular in association with MHS-predisposing *RYR1* mutations. At the other end of the spectrum, severe neonatal manifestations associated with both (often *de novo*) dominant and recessive *RYR1* mutations have been reported [3-4]. In these patients decreased fetal movements, arthrogryposis multiplex congenita (AMC), polyhydramnios, scoliosis and respiratory distress are typically observed [1, 3-4, 19]. Recently, several cases with a lethal neonatal course have been documented [20], some of those within the spectrum of the “lethal multiple pterygium syndrome” [5]. Intrafamilial phenotypic variability has been reported in several families affected by such severe presentations [4, 20].

Lately, bleeding abnormalities have been described in patients with *RYR1* mutations, in particular mutations also associated with the MHS trait and/or ERM [21]. This clinically relevant observation was confirmed and its molecular basis elucidated in an animal model of *RYR1*-associated malignant hyperthermia, the Y522S mouse [21]. Here we report complications of unexpectedly severe CNS bleeding in an infant with *RYR1*-associated AMC and a complex myopathic pattern comprising dystrophic features and eccentric cores on muscle biopsy.

## Case report

This male infant was born to healthy non-consanguineous parents. The mother had previously lost a fetus in the 8<sup>th</sup> week of pregnancy. Pregnancy was complicated by polyhydramnios. Prenatal ultrasound suggested pulmonary hypoplasia. At 32 weeks gestation Caesarean section was performed due to premature rupture of membranes. Apgar score at 1 minute was 5 and ventilation was immediately instituted due to insufficient respiratory effort. Umbilical artery pH value was normal at

pH 7.39. Growth parameters were reduced for gestational age (birth weight 1240g-3th percentile, length 33cm- accurate measurements hindered by extensive limb contractures) with head circumference within normal range (31.5 cm-90<sup>th</sup> percentile). The patient presented with arthrogryposis multiplex and extreme muscular hypertonia. Deep tendon reflexes were absent. Serum creatine kinase was within the normal range (230 IU/l and below on repeated controls). Thoracic rigidity and scoliosis confounded respiratory impairment and impeded successful mechanical ventilation. Additional dysmorphic features including camptodactyly, high forehead, narrow palpebral fissure, deep set eyes, long philtrum, small mouth with high palate and discrete retrognathia were noted (Fig.1).

Using high frequency oscillation ventilation (HFO) respiratory parameters could be temporarily stabilized, but change to conventional modes of ventilation was not tolerated until the 14th day of life. CT scan of the lungs did not reveal any specific pulmonary abnormality. Subsequently, Neurally Adjusted Ventilatory Assist (NAVA) ventilation was successfully introduced and tolerated. At the age of 7 months tracheotomy had to be performed to enable ambulatory assisted ventilation and home care.

Cranial MRI at the age of 8 weeks showed sequelae of a 2° hemorrhage arising from the left caudothalamic groove as well as a spinal epidural space-occupying lesion from cervical spine 5 to thoracic spine 9, suggesting an organized prenatal hemorrhage (Fig.2). Progressively abnormal increase in head circumference led to the diagnosis of post-hemorrhagic hydrocephalus internus, presumably caused by prenatal intracranial hemorrhage and confirmed on cranial ultrasound. Ventriculo-peritoneal shunting was performed at the age of 4 months.

Chromosomal analysis and molecular genetic analysis of *SMN1*, *IGHMBP2*, *MTM1* and *DMPK* genes excluded the clinically most relevant differential diagnoses.

Histopathological analysis of a diagnostic muscle biopsy taken at the age of 4 months from the vastus lateralis muscle showed complex myopathological features comprising increased endo- and perimysial connective and fatty tissue, rounding of muscle fibers with pathological fiber size variation, internalization of myonuclei as well as few degenerating fibers. Further, histochemical stains identified: 1) multiple fibers with eccentric cores, 2) fibers with focal accumulation of glycogen, 3) fibers with focal increase of acidic phosphatase reaction, and 4) multiple fibers with attenuated COX and SDH-enzyme reactivity (Fig.3). Biochemically, deficiency of mitochondrial respiratory chain complex I was found. However, as clinical signs and clinical course differed from complex-I-associated infantile myopathies, molecular genetic diagnostics were extended.

Exome sequencing revealed compound heterozygous mutations in the ryanodine receptor (*RYR1*) gene (c.6488G>A, p.(Arg2163His); c.14918C>T, p.(Pro4973Leu)). No other variants were detected in genes related to arthrogryposis or increased bleeding risks. Genetic analysis of the parents confirmed recessive inheritance, showing heterozygosity for the (p.(Pro4973Leu)) mutation in the father and for the (p.(Arg2163His)) mutation in the mother.

Genetic counseling of the young family was performed and additional genetic testing was arranged for other family members, especially with regards to the possibly increased malignant hyperthermia susceptibility (MHS) risk. On specific questioning, the parents reported cosegregation of the familial *RYR1* mutations with variable degree of ptosis on both sides of the family, and increased sweating on the maternal side.

The patient continued to make developmental progress but remained severely delayed, with part range antigravity movements only in the limbs. He required



percutaneous endoscopic gastrostomy (PEG) feeding and mechanical home ventilation.

## Discussion

*RYR1* mutations are associated with the malignant hyperthermia susceptibility (MHS) trait as well as a wide range of myopathies with variable clinico-pathological features. Severe forms of fetal akinesia, occasionally associated with neonatal lethality, represent the most severe end of the *RYR1*-associated spectrum and, so far, have only been reported in a limited number of patients [1, 3-4].

Here we report a patient with a severe *RYR1*-associated early-onset myopathy, comprising features of arthrogryposis multiplex congenita (AMC), profound respiratory impairment and additional evidence of CNS bleeding of prenatal origin. In terms of overall severity, our patient falls within the severe end of recessive *RYR1*-related myopathies, where patients may be premature and present with breathing and feeding difficulties requiring ventilation support and gastrostomy feeds [1, 3, 22].

The patient was found to be compound heterozygous for a maternally inherited *RYR1* c.6488G>A mutation, previously associated with MHS and cores on muscle biopsy [23], and a paternally inherited *RYR1* c.14918C>T mutation also previously implicated in the MHS trait [24-25] supporting the notion that some *RYR1* mutations behave as dominants with regards to the MHS trait but as recessives with regards to congenital myopathy phenotypes [7, 26]. Exome sequencing did not show any other mutations in our patient. Recessive *RYR1*-related myopathies are predominantly due to compound heterozygosity for *RYR1* loss-of-function mutations and missense mutations, the latter also occasionally associated with the MHS trait [7-8, 15]. Compound heterozygosity or homozygosity for MHS-associated *RYR1* mutations is less common, but has been reported in some patients with widely variable clinical-

pathologic features [26-27] sometimes distinct from other forms of recessive *RYR1*-related myopathies. Another distinct phenotype associated with MHS mutations is the King-Denborough syndrome (KDS) [28], a dysmorphic myopathic syndrome characterized by ptosis, short stature, scoliosis and a predisposition to often sporadic MHS episodes.

Interestingly, our patient had additional features of two-stage CNS bleeding events that for several reasons are more likely to be due to his genetic background rather than his gestation: Firstly, prenatal intraventricular hemorrhage (IVH) is common in very preterm infants but incidence decreases with advancing gestational age and becomes increasingly rare after 32 weeks gestation [29]. Secondly, epidural hematoma affecting the brain is uncommon after atraumatic birth [30] and exceedingly rare in the spinal cord. Thirdly, Lopez et al. recently reported evidence for an increased bleeding tendency in *RYR1*-mutated patients [21] in whom other coagulation defects had been excluded, supporting the hypothesis of a similar genetic predisposition also in our patient. Interestingly, all of the patients reported by Lopez et al. were either heterozygous or compound heterozygous for *RYR1* mutations implicated in the MHS trait, corresponding to the genotype also identified in our patient and in keeping with previous case reports of increased bleeding in patients with MHS [31-33]. Lopez et al. also demonstrated prolonged bleeding in the mouse model heterozygous for the *RYR1* Y522S MHS mutation, and confirmed reduced vascular smooth muscle cell contractility as the pathophysiological cause for this observation [21]. Interestingly, mice homozygous for the *RYR1* Y522S mutation have signs of an antenatal bleeding disorder presenting with marked subcutaneous bleeding and edema at birth. Moreover, a role of the *RYR1* receptor in CNS vasoregulation is also supported indirectly by the recognized beneficial role of the

specific RYR1 antagonist dantrolene in the management of subarachnoid hemorrhage and other traumatic CNS events with a vascular component [34-35].

We conclude that this report adds to the phenotypic variability of *RYR1* mutations and may draw the attention of clinicians and researchers to the possibility of hemorrhagic complications associated with *RYR1* mutations.

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**Figure 1.** Clinical features of the patient at birth and at 6 months of age. Initially contractures of upper and lower limbs were present (insert) while facial dysmorphic features consisted of high forehead, narrow palpebral fissure, deep-set eyes, long philtrum, small mouth and retrognathia.

**Figure 2.** MRI of the brain (A) and the spinal canal (B) at the age of two months.

(A) Axial Susceptibility Weighted Imaging (SWI) at the level of the lateral ventricles detects blood deposits in the left caudothalamic groove (white arrow), on both sides of the choroid plexus (asterisk), along the inner surface of the left posterior horn as well as in the left Sylvian fissure (arrowheads). In addition, blood breakdown products can be seen in the dorsal portion of the longitudinal cerebral fissure (black arrow).

(B) Sagittal T2-weighted image demonstrates a space-occupying lesion with heterogeneous signal abnormality in the dorsal part of the thoracic spinal canal, indicating a chronic epidural hemorrhage (arrows). Note partial compression and anterior displacement of the spinal cord (asterisk).

**Figure 3.** Skeletal muscle pathology in the reported *RYR1* patient. Skeletal muscle sections from the patient were stained by HE (A), NADH (B) and COX/SDH (C). Note the rounding of muscle fibers with marked variation in fiber size and increased connective tissue (A). NADH and COX/SDH stainings depict numerous eccentric cores (B/C). Scale bar = 100  $\mu$ m.

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Patient name: Preiß, ConstantinDate: 15/02/2017☒ check here if minor or unable to provide consent

I consent for medical photographs to be made of me or my child (or person for whom I am legal guardian). I understand that the information may be used in my medical record, for purposes of medical teaching, or for publication in medical textbooks or journals as I have designated below. By consenting to these medical photographs I understand that I will not receive payment from any party. Refusal to consent to photographs will in no way affect the medical care I will receive. If I have any questions or wish to withdraw my consent in the future I may contact:

Prof. Dr. med. Regina Trollmann, Kinderklinik, Universitätsklinikum Erlangen
--

By signing this form below I confirm that this consent form has been explained to me in terms which I understand.

I consent for these photographs to be used in medical publications, including medical journals, textbooks, and electronic publications. I understand that the image may be seen by members of the general public, in addition to scientists and medical researchers that regularly use these publications in their professional education. Although these photographs will be used without identifying information such as my name, I understand that it is possible that someone may recognize me. I also agree for my image to be shown for teaching purposes and to be used for my medical record.

3/Preiß (Signature) 3/Preiß (Witness)  
H. Trollmann  
RTD

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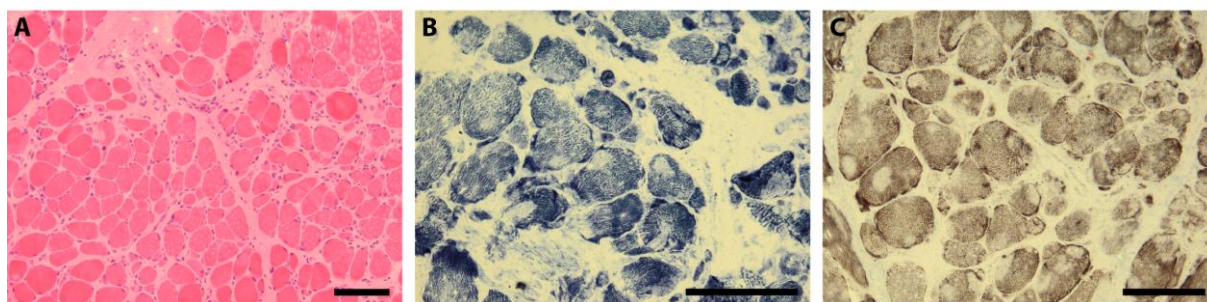


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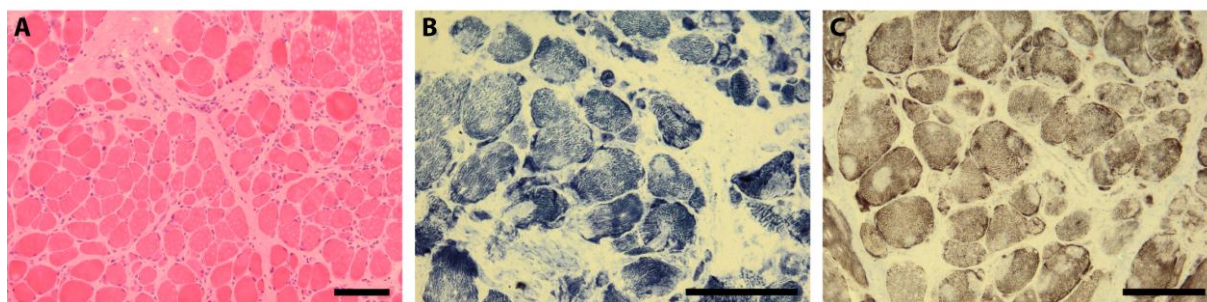


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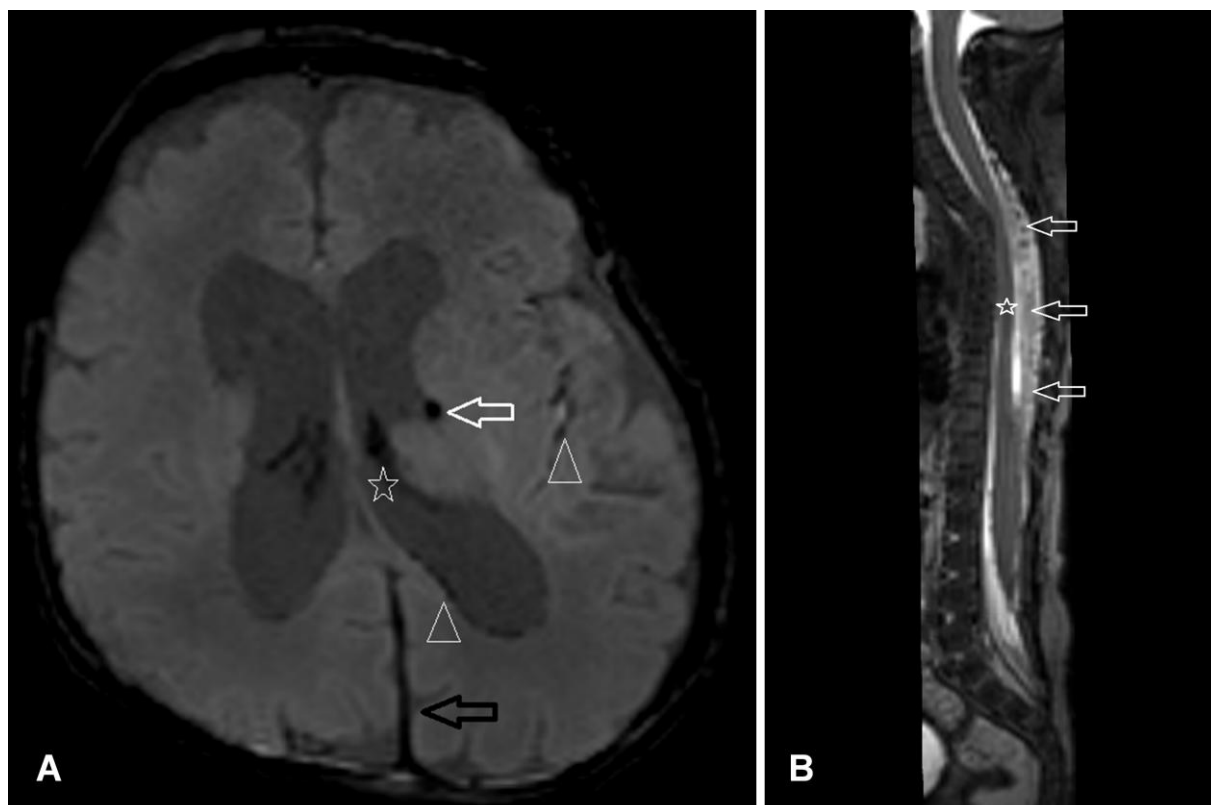
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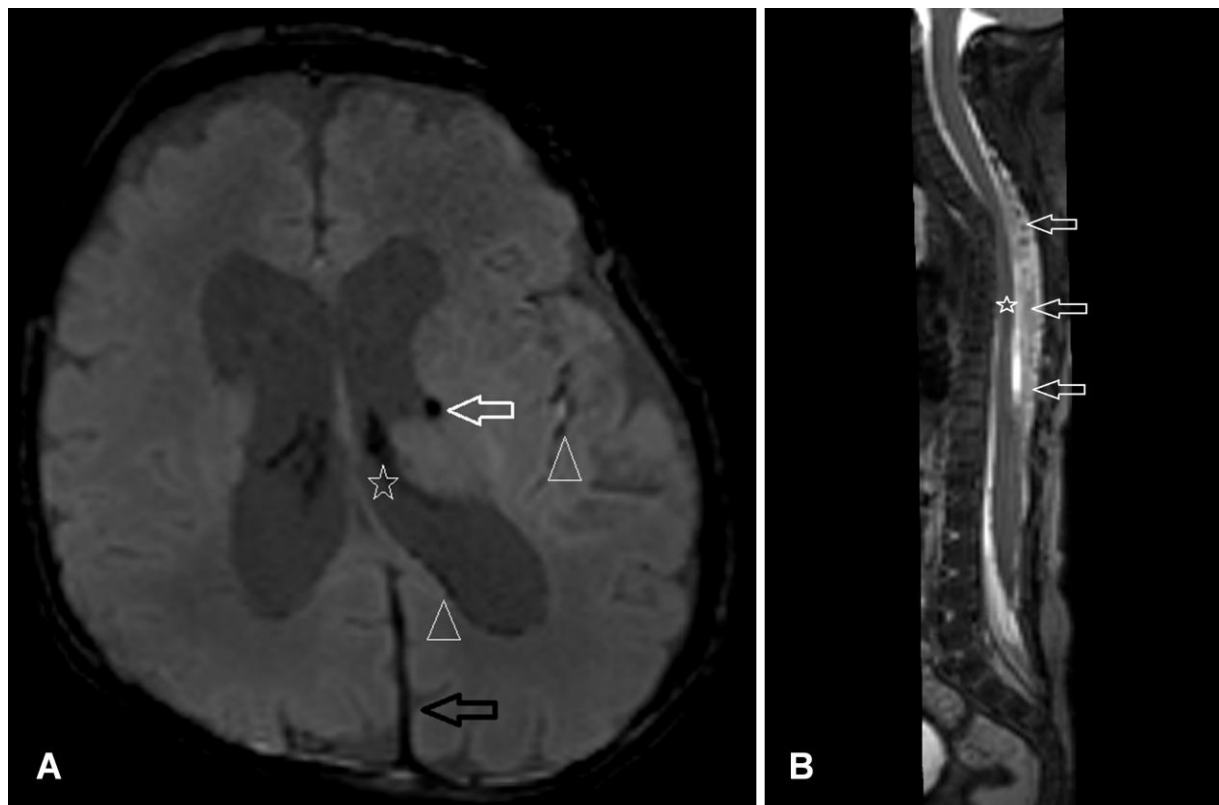


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